Rhabdoviridae
Rabies virus

Rabies is an acute infection of the CNS that is almost always fatal (99%). The virus is usually transmitted to human from the bite of a rabid animal. Although the number of cases is small, rabies is a major public health problem, because it is wide spread among animals reservoirs. Only one antigenic type of rabies virus is known.

Important properties of rhabdoviridae:

Virion: Bullet-shaped, 75X 180 nm.

Genome: ssRNA, negative sense, linear, nonsegmented.

Protein: One envelop glycoprotein

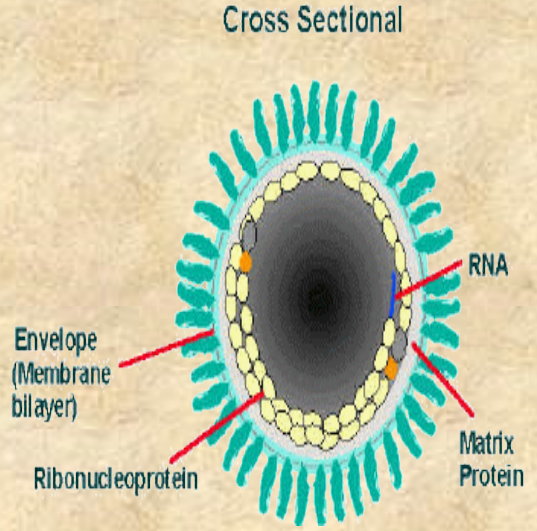
Envelope: present

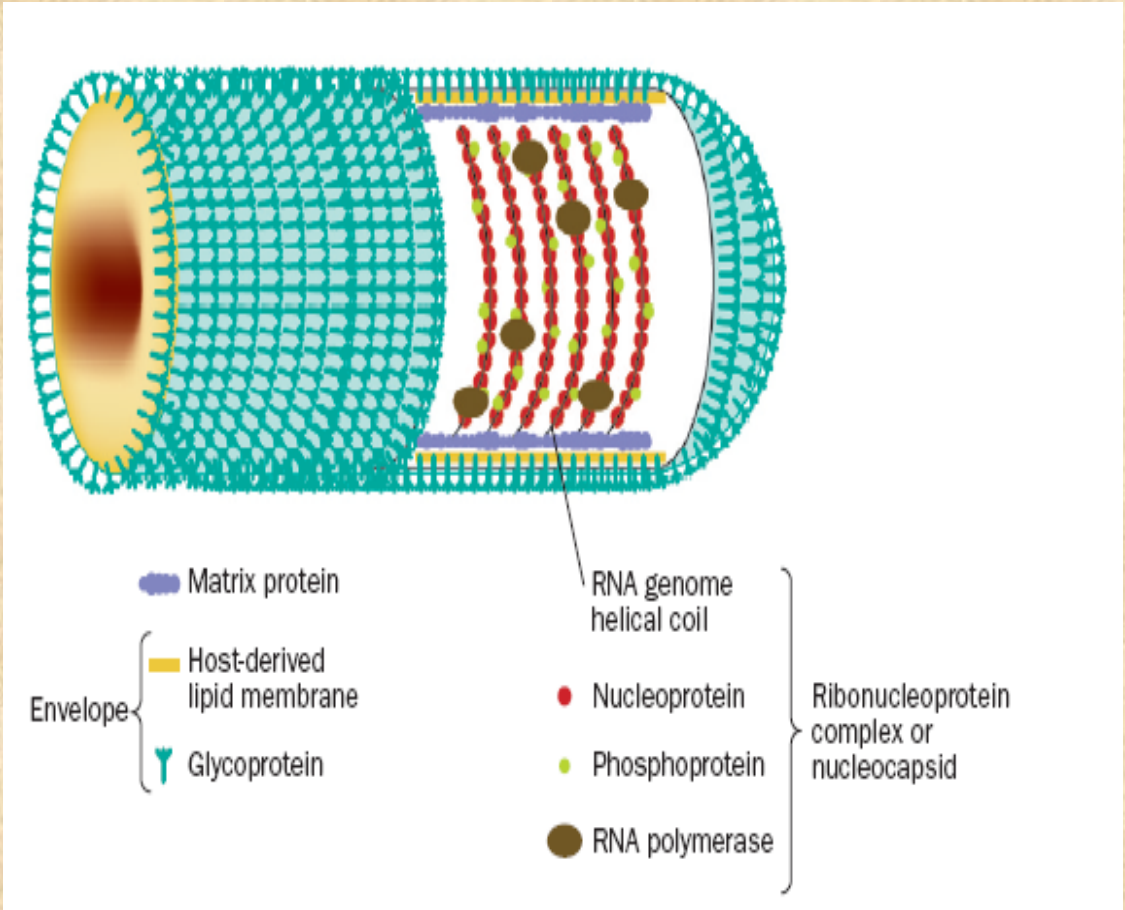
Replication: cytplasmic, virion bud through plama membrane.

Outstanding characteristics: wide host range, high fatality rate.

The RNA genome of the virus encodes five genes whose order is highly conserved: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and the viral RNA polymerase (L).

Rabies virus structure



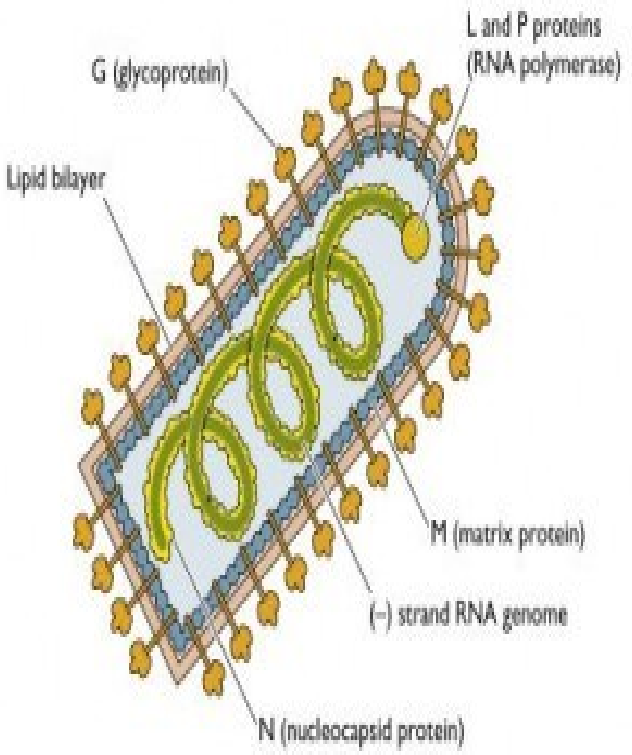


Replication cycle & routes of infection

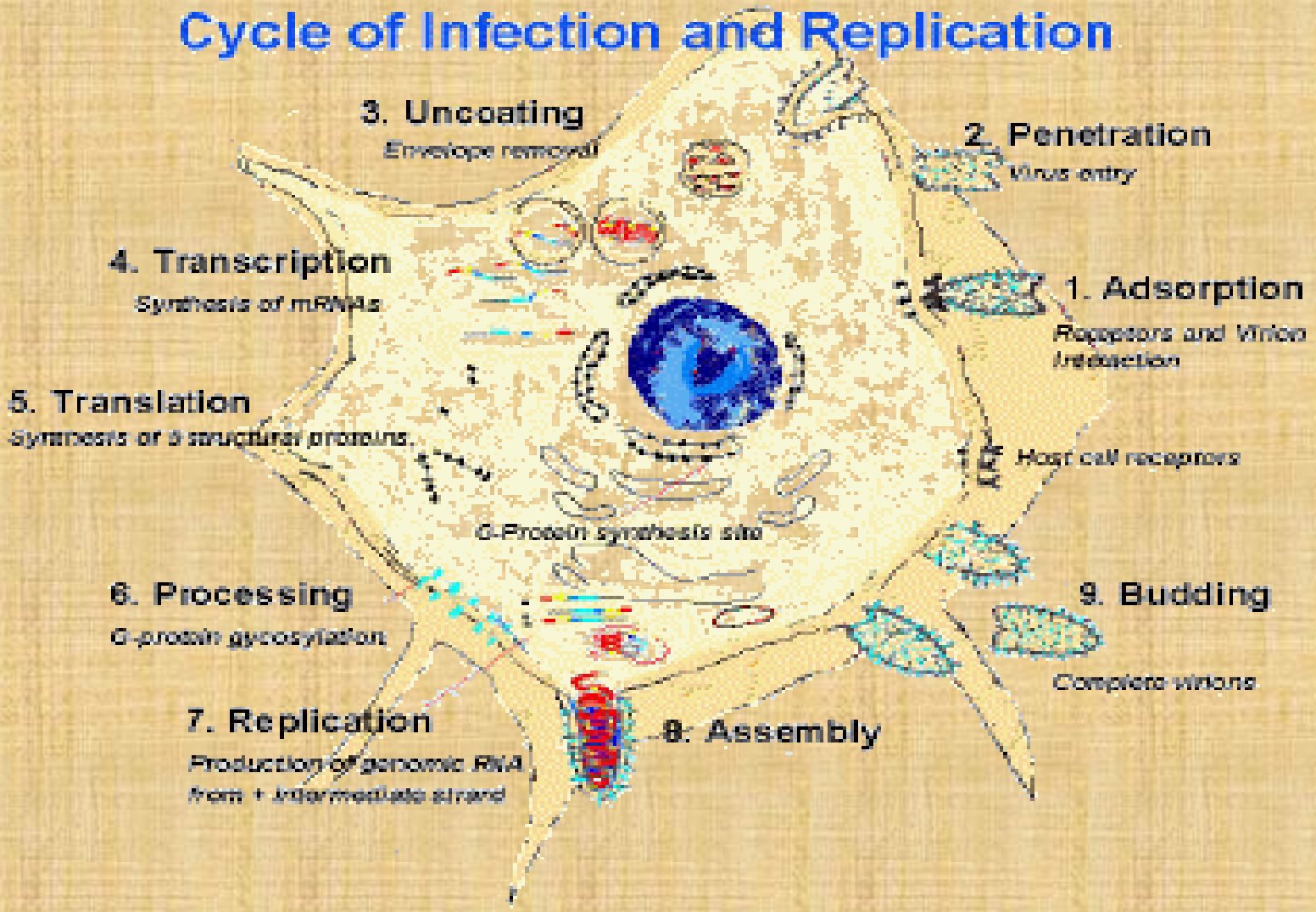
Rabies virus attached to cells via its glycoprotein spikes; the nicotinic acetylcholin receptor may serves as a cellular receptor. The five viral proteins and single strand RNA are released into the cytoplasm. The L protein then transcribes five mRNA strands and a positive strand of RNA all from the original negative strand RNA using free nucleotides in the cytoplasm. These five mRNA strands are then translated into their corresponding proteins (P, L, N, G and M proteins) at free ribosomes in the cytoplasm.

The viral **negative sense** genomic RNA is transcribed by the virion associated RNA polymerase into **positive sense** RNA, which then serves as a template for synthesis of viral genome plus mRNA that gives rise to viral proteins. Negative sense viral RNA becomes incorporated with nucleocapsid & join to matrix protein at cell surface, then budding occurs.

Rabies virus has a wide host range & it is widely distributed in infected animals, especially in CNS, saliva, urine, milk, lymph & blood. Recovery from infection is rare.



Replication cycle of rabies virus



The virus can penetrate broken skin & intact mucous membranes. Humans are usually infected when a bite of rabid animal inoculates virus-laden saliva through the skin. There is also risk of infection from being scratched or even licked if the skin is broken. Human rabies result from inhalation is rate. Transmission between humans is extremely rare. Rabies is an example of a viral pathogen modifying the behavior of its host to facilitate its transmission to other hosts.

Host range: Rabies virus has a wide host range. All warm-blooded animals including humans can be infected. Susceptibility varying among mammalian species ranging from very high (foxes, jackls, wolves) to high (skunks, raccoons, cats, bats, rabbits, cattle) to moderate (Dogs, sheep, goats, horses) to low (opossums).

When freshly isolated in the laboratory, the strain referred to as "street virus" which show long incubation period (21-60 days in dogs) & regularly produce intracytoplasmic inclusion bodies. Several brain to brain passage in rabbit yield a "fixed or mutant" virus with short incubation period (4-6 days), & less frequently formation of inclusion bodies.

Animal species

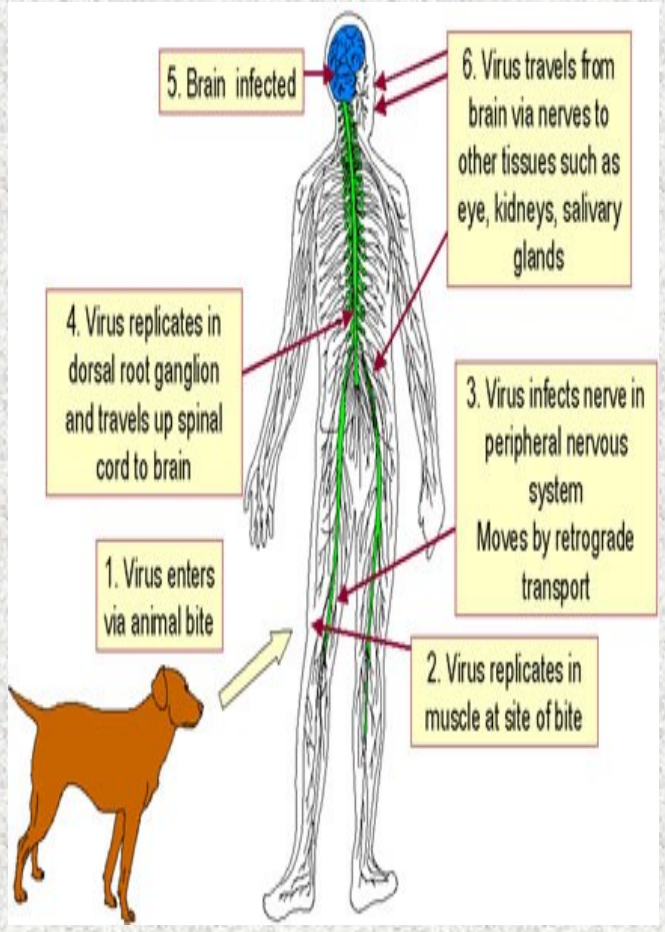
Pathogenesis & pathology

Rabies virus multiplies in muscles or connective tissues at the site of inoculation & then enters peripheral nerves at neuromascular junction & spread up through the afferent nerves to the CNS. The surface glycoprotein is the major factor in rabies virus neuroinvassiveness & pathogenicity (a mutation in this glycoprotein result in loss of virulence). Purified spikes containing the viral glycoprotein elicit neutralizing antibodies in animal.

The virus multiply in the brain causing encephalitis & then spread through peripheral nerves to the salivary glands & other tissues (pancreas, kidney, retina, heart). Rabies has not been isolates from the blood of infected person.

Susceptibility to infection & the incubation period may depend on the host's age, genetic background, & immune Status, the viral strain involved, the amount of the inoculum, the severity of laceration & site of bite.

Rabies virus produce specific eosinophilic cytoplasmic inclusion, the Negri body, in infected nerve cells, These are filled with virus nucleocapsid. The presence of such inclusions are pathognomonic for rabies (Absence in 20% of cases).



Clinical findings

Rabies is a primarily a disease of animals. The disease is an acute, fulminant, fatal encephalitis. The incubation period in human is typically 1-2 months. The clinical spectrum can be divided into three phases:

- The prodrome: which lasts for 2-10 days, characterized by non-specific syndrome & photophobia.
- furious rabies : The acute neurological phase: patients show signs of NS dysfunction, increased salivation & lacrimation & hydrophobia.
- Convulsive phase: Seizures or coma & death usually 2-7 days after the onset of neurological signs. The major cause of death is respiratory paralysis.

The usual incubation period in dogs ranges from 3-8 weeks, but may as short as 10 days. Clinically it is divided into the same three phases as in human rabies.

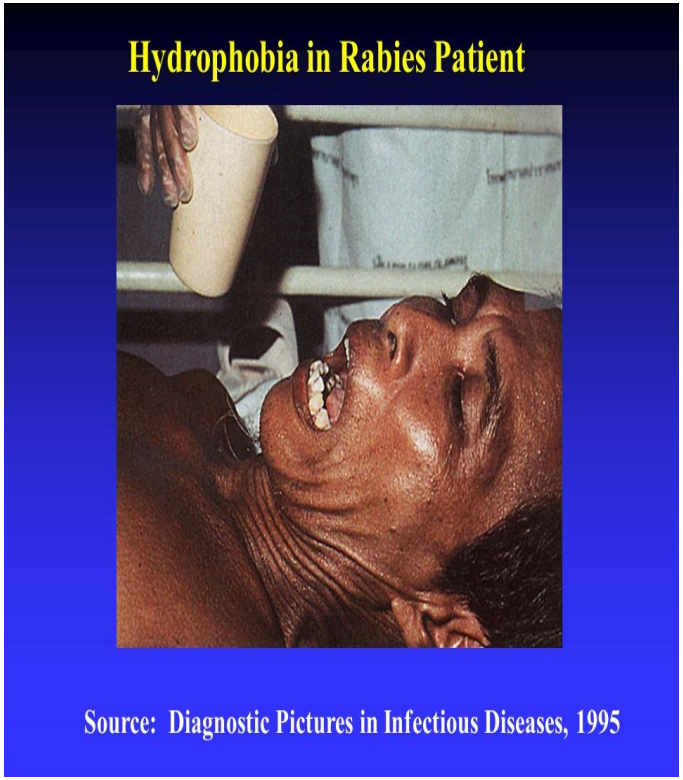
Hydrophobia

Hydrophobia (fear of water) is the historic name for rabies. It refers to a set of symptoms in the later stages of an infection in which the person has difficulty swallowing, shows panic when presented with liquids to drink, and cannot quench his thirst. Any mammals infected with the virus may demonstrate hydrophobia.

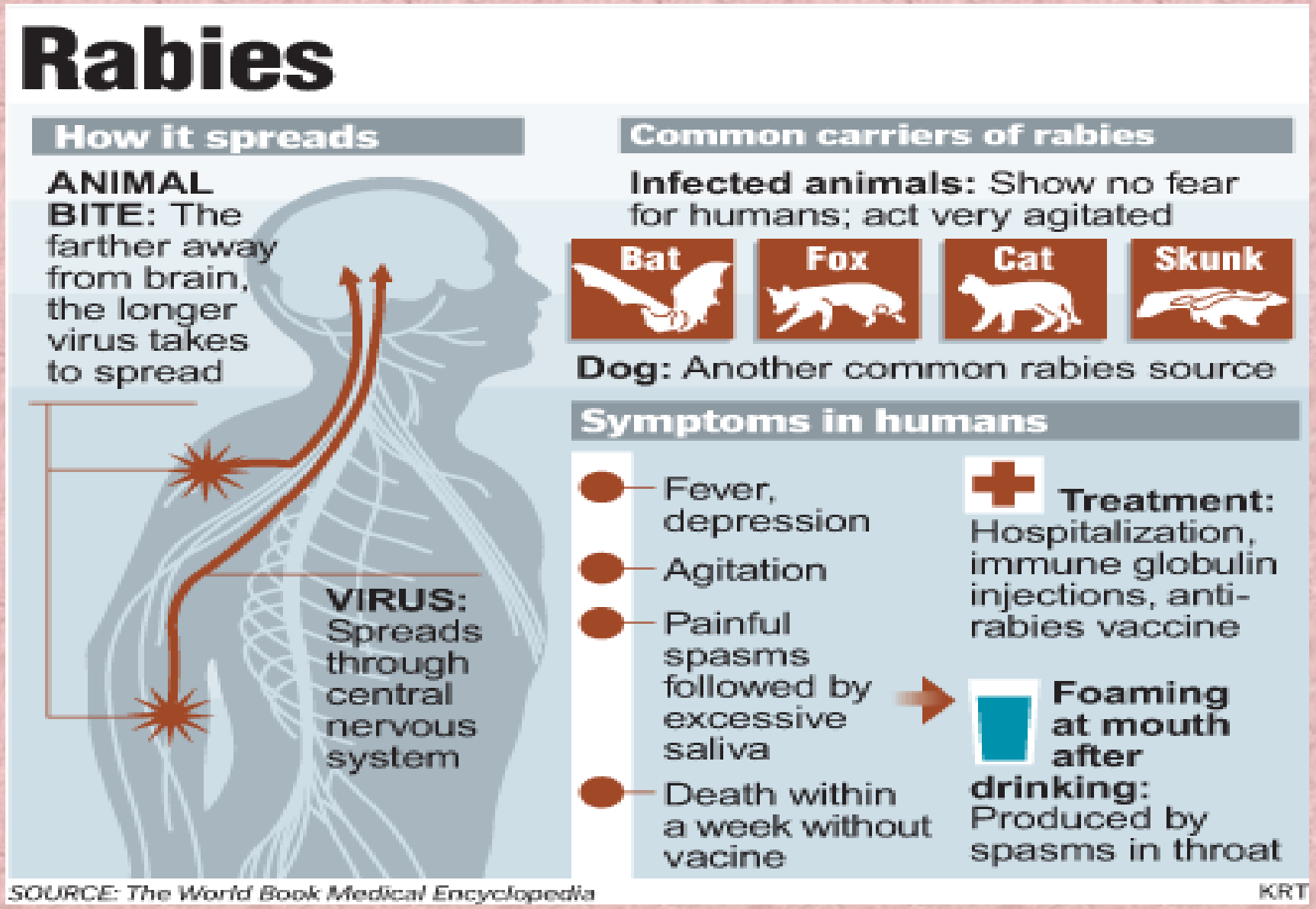
Saliva production is greatly increased, and attempts to drink, or even the intention or suggestion of drinking, may cause **excruciatingly painful spasms** of the muscles in **the throat and larynx**. This can be attributed to the fact that the virus multiplies and assimilates in the salivary glands of the infected animal for the purpose of further transmission through biting. The animal's ability to transmit the virus would reduce significantly if it could swallow saliva and water.

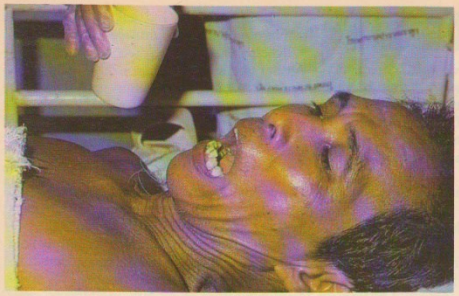
Hydrophobia is commonly associated with **furious rabies** that affects 80% of the infected people. The remaining 20% may experience a **paralytic form** of rabies that is marked by muscle weakness, loss of sensation, and paralysis. This form of rabies does not usually cause fear of water.

Clinical findings

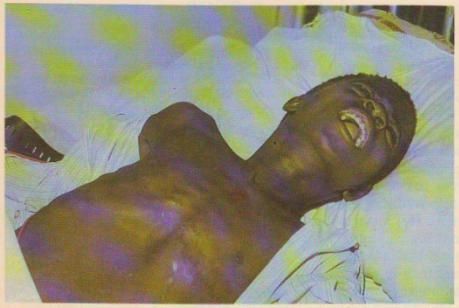


Clinical findings

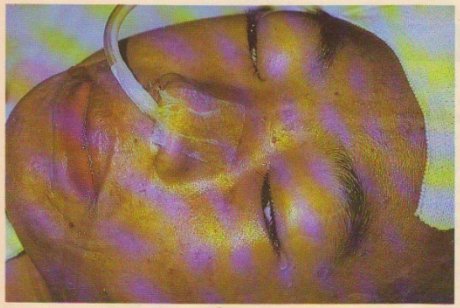




6 Hydrophobic spasm in a 50-year-old Thai man with furious rabies. He asked for water, but when it was offered there was spasm of inspiratory muscles producing a violent gasp associated with inexplicable terror. A similar response was induced by fanning (aerophobia).



7 Hydrophobic spasm ending in opisthotonos in a 14-year-old Nigerian boy with furious rabies.



8 Facial spasm, hypersalivation and lacrimation in a 14-year-old Thai boy with furious rabies, who was receiving intensive care.

Figures 6, 7 and 8 copyright Dr D A Warrell.

paralytic rabies will develop, depending on whether the brain or spinal cord is predominantly infected.

Furious rabies is characterized by hydrophobia which is a combination of inspiratory muscle spasm and terror in response to attempts to drink water (Figure 6). Various other external stimuli can excite the reaction, including a draught of air (aerophobia) and the sight, sound or mere mention of water. Hydrophobic spasms may end in opisthotonos (Figure 7) and generalized convulsions; death results from respiratory or cardiac arrest. Also typical of furious rabies are periods of excitation, during which the patient becomes wild, hallucinated and fugitive, alternating with lucid intervals. Other features include:

- meningism
- cranial nerve lesions
- spasticity
- involuntary movements
- fluctuating body temperature
- signs of autonomic hyperactivity, for example, salivation, lacrimation, sweating and tachycardia (Figure 8).

Without intensive care, about 35% of patients will die during a hydrophobic spasm in the first few days. The remainder lapse into coma and generalized flaccid paralysis, and seldom survive for more than 1 week.

Paralytic rabies is seen in about 20% of cases, especially in those bitten by vampire bats. Flaccid paralysis often begins in the bitten limb and ascends symmetrically or asymmetrically until it involves the muscles of deglutition and respiration. Fasciculation and sensory disturbances also occur. The patient dies within 2–3 weeks.

Hydrophobia is unusual, but a few spasms occur late in the illness.

Laboratory diagnosis

Rabies can be confirmed in the animal responsible for the bite within a few hours by immunofluorescence of brain impression smears or histological examination for Negri bodies and, after about 2 weeks, by intracerebral inoculation of mice with a suspension of the animal's brain tissue.

In patients, rabies can be confirmed early in the illness by immunofluorescence of skin biopsy or brain biopsy, and by virus isolation from saliva and other secretions. Immunofluorescence of corneal impression smears has proved unreliable. Fluorescent and other antibodies are not usually detectable in serum or CSF before the eighth day. The discovery of CSF antibody suggests rabies rather than post-vaccinal encephalitis.

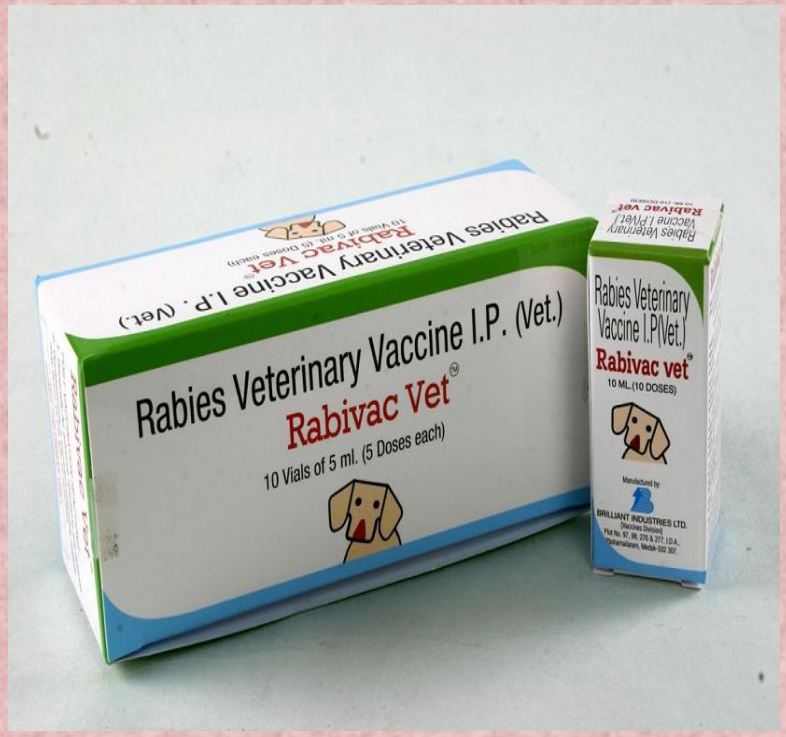
Clinical findings

Laboratory diagnosis

1. Rabies antigens or nucleic acid: tissues infected with rabies virus are identified rapidly & accurately by immunofluorescent or Immunoperoxidase staining using antirabies monoclonal antibodies [impression from the brain or the cornea often used].
2. RT-PCR can be used from fixed or unfixed brain tissue.
3. Identification of Negri bodies in the brain or spinal cord of both humans & animal by IF.
4. Viral isolation.
5. Serology: serum antibodies can be detected by IF, neutralization & complement fixation tests. Antibodies in CSF are produced in rabies infected individuals but not in response to vaccination.
6. Animal observation.

Immunization

The action of passively administered antirabies antibodies is to neutralize some of the inoculated virus & to lower its concentration in the body, providing additional time for a vaccine to stimulate active antibody production to prevent entry to CNS.



Types of vaccines:

1. Human diploid cell vaccine (HDCV)
2. Adsorbed rabies vaccine (RAV)

The HDCV & RAV are equally effective & safe.

3. Nerve tissue vaccine
4. Duck embryo vaccine

Types of rabies antisera:

1. Rabies immunoglobulin, Human (HRIG)
2. Antirabies serum, equine

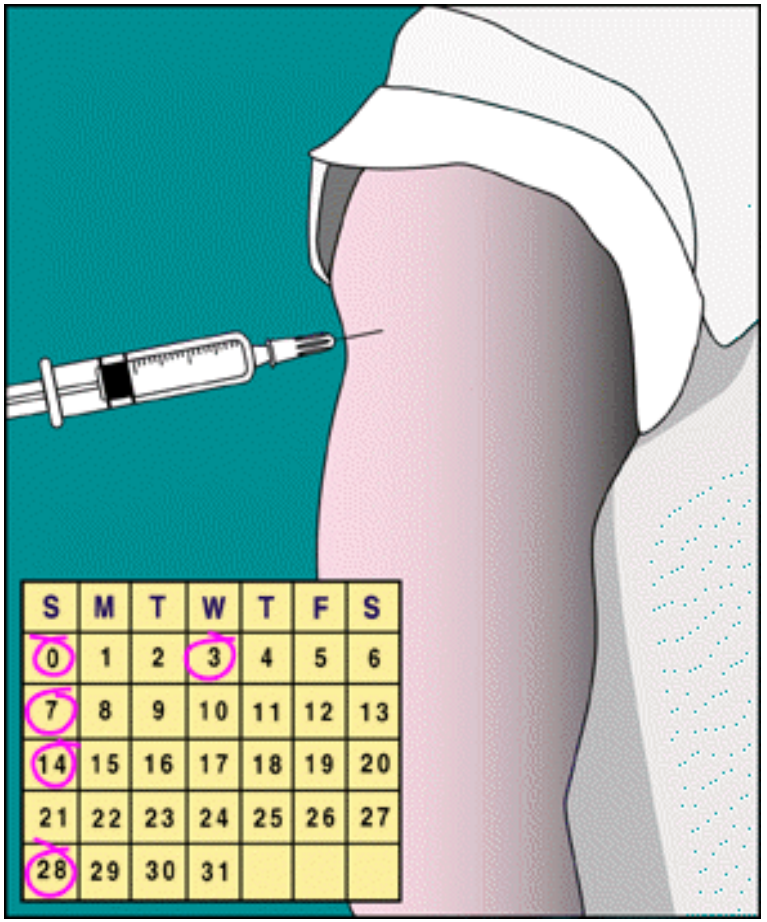
Vaccination

Preexposure prophylaxis :

For parsons with special risk of exposure to rabies. It consist of immunization with either HDCV or RAV vaccine[1.0 ml, IM (deltoid) at 0,7,21, or 28 day with booster dose at day 0 (depend on the exposure risk category].

Postexposure prophylaxis:

For persons exposed to rabies virus. It consist of the immediate thorough cleaning of all wounds with soap & water. Irrigation with virucidal agent (70% alcohol, povidone iodine). Administration of rabies immuno globulin, & for persons not previously vaccinated, the administration of either HDCV or EAV vaccine [1.0 ml, IM (deltoid) on 0,7,14, & 28 days].



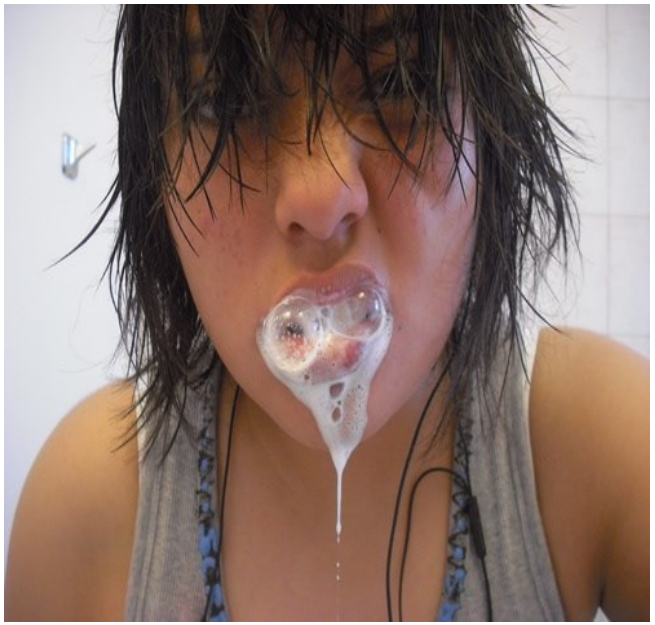
Epidemiology

In 2010, an estimated 26,000 people died from rabies. The majority of the deaths occurred in Asia and Africa. India has the highest rate of human rabies in the world, primarily because of stray dogs. An estimated 20,000 people die every year from rabies in India — more than a third of the global toll.

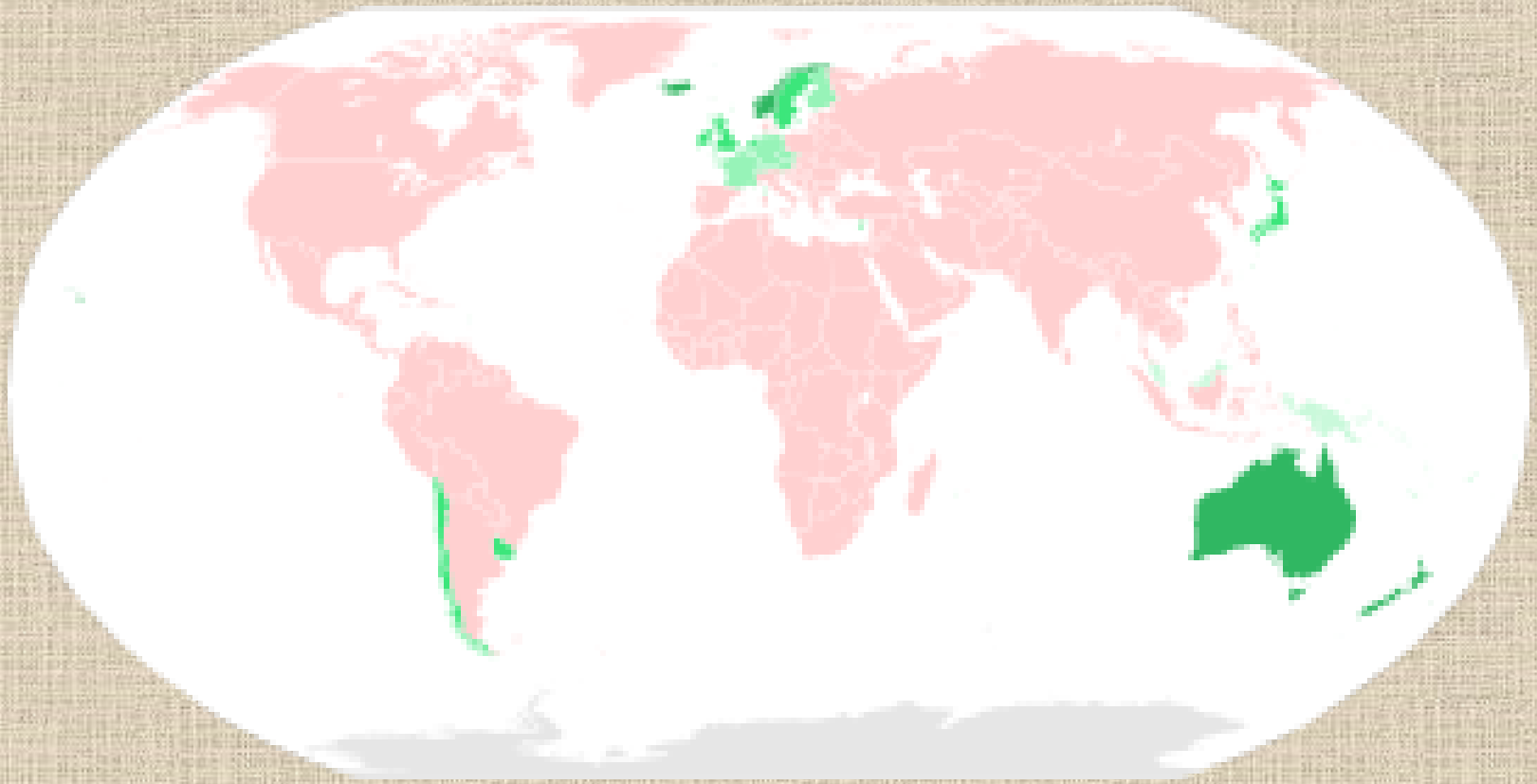
The rabies virus survives in widespread, varied, rural reservoirs. It is present in the animal populations of almost every country in the world except Australia and New Zealand.

In Asia and in parts of the Americas and Africa, dogs remain the principal host. Mandatory vaccination of animals is less effective in rural areas. Especially in developing countries. Rabies is common among wild animals in the US. Bats, raccoons, skunks and foxes account for almost all reported cases (98% in 2009). Rabid bats are found in all 48 contiguous states.

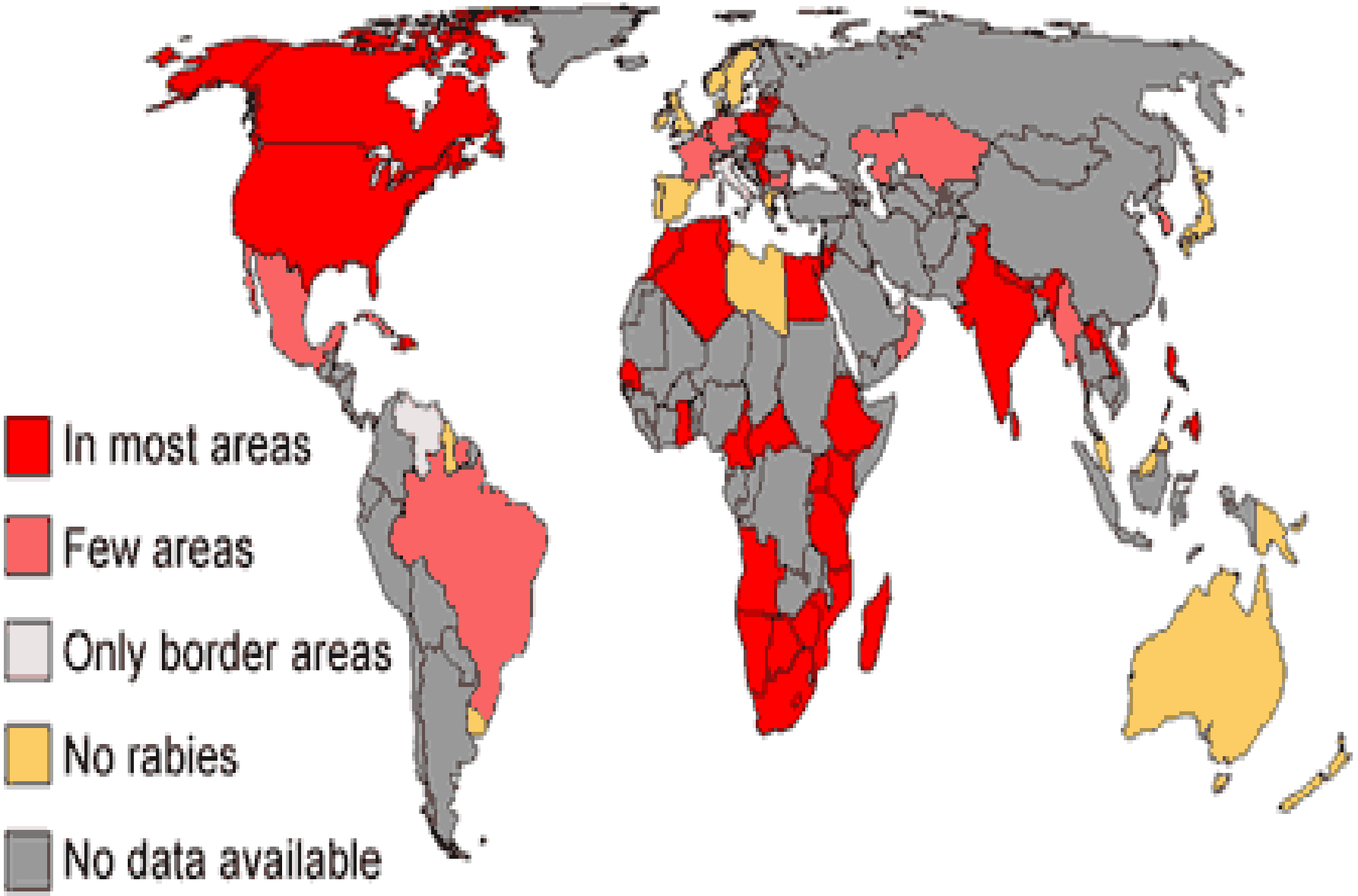
In unvaccinated humans, rabies is almost always fatal after neurological symptoms have developed . Vaccination after exposure, PEP, is highly successful in preventing the disease if administered promptly, in general within 6 days of infection. with no delay, PEP is 100% effective against rabies.



Countries free from Rabies (in green)



Rabies in animals



Lyssavirus Host Animals Found Around the World

Rabies


5 Virus reaches brain and causes fatal encephalitis.
6 Virus enters salivary glands and other organs of victim.
4 Virus ascends spinal cord.
3 Virus moves up peripheral nervous system to CNS.
2 Virus replicates in muscle near bite.
1 Virus enters tissue from saliva of biting animal.